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Phase I and pharmacology study of flavone acetic acid administered two or three times weekly without alkalinization

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Abstract Flavone acetic acid (FAA, NSC 347512) is a synthetic flavonoid compound with a unique form of preclinical antitumor activity, but its mechanism of action is still not known. In an attempt to exploit the remarkable preclinical activity of this compound in such a way as to allow its use as a clinically useful agent, we performed a phase I and pharmacology study with frequent administration and no hyperhydration or alkalinization. Sixteen patients (9 men, 7 women) were given FAA as 6-h i.v. infusions 2 or 3 times a week (10 and 6 patients, respectively), at doses ranging from 2.5 to 8.1 g/m^2. A total of 130 doses were administered during this study. Sedation, arterial hypotension, vomiting and diarrhea were the predominant toxicities observed at the highest dose (8.1 g/m^2). One patient developed severe but reversible multiple organ failure. No treatment-related deaths occurred. Pharmacokinetics was linear for the doses studied, with peak plasma levels ranging from 39 to 449 μg/ml and a mean terminal half-life of 3.1 h. No drug accumulation was observed with this frequent-administration schedule. No objective response was observed. Three FAA infusions per week at 8.1 g/m^2 could be recommended as an optimal and tolerable schedule.

Key words Flavone acetic acid · Phase I trial
Pharmacokinetics

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Dedicated to the memory of Dr. Marcel de Forni (deceased on 10 May 1994)

Introduction

Flavone-8-acetic acid (FAA; NSC 347512) is a synthetic flavonoid compound with a unique pattern of preclinical antitumor activity. FAA has demonstrated excellent activity against a broad spectrum of slow-growing murine solid tumors (colon, pancreatic and mammary adenocarcinomas, Glasgow osteogenic sarcoma) that are usually insensitive to most cytotoxic drugs [1–3]. In contrast to its solid tumor activity, FAA has exhibited poor activity against murine leukemia cell lines (P388, L1210) and human tumor xenografts in nude mice. A similar pattern of selective cytotoxicity against solid tumors was observed in a soft agar colony formation assay [1]. FAA's precise mechanism of anticancer activity is presently poorly understood [4]. Factors involved in the mechanism of action of this drug include the tumor vasculature [5], platelet functions [6], biotransformation [7] and the immune system [8, 9]. Tumor DNA damage has also been observed after in vivo administration in mice [10].

Pharmacological and toxicological studies in animals have shown that FAA has unusual kinetic features. The plasma clearance of the drug is lower in mice than in dogs. A steep dose-lethality curve was observed in mice and suggested a peak plasma concentration (>600 μg/ml) causing acute toxicity problems [11]. Stupor was the symptom most commonly observed in mice after a single i.v. injection of the LD_{10}. Gastrointestinal distress was an additional dose-limiting toxicity in dogs. No myelosuppression was observed. Since the preclinical activity of FAA has been found to vary with administration schedule and duration of exposure, it seems that an intermittent i.v. schedule might be the best mode of drug delivery [1].

Previous phase I studies were performed using different durations of infusion (1–12 h) and different intervals for drug administration (1–3 weeks) [12–15]. Hyperhydration and alkalinization were frequently recommended with the aim of preventing tubular drug precipitation, with the possible risk of interfering with potential antitumor activity. Arterial hypotension and diarrhea were the dose-limiting

toxicities in a weekly 6-h infusion schedule at a dose of 10 g/m^2 [12].

In cognizance of the above preclinical and clinical information, we conducted a phase I and pharmacokinetic study of FAA administered in 6-h infusions 2 or 3 times a week, without hyperhydration or alkalinization. The aims of this phase I trial were to define FAA toxicities using this scheme of administration and to optimize FAA weekly administration in the light of both clinical and pharmacokinetic findings.

Patients and methods

Patient selection

Selected patients who had histologically confirmed advanced malignancies but were without standard alternative treatments were entered in this phase I study. Eligibility criteria included: age between 18 and 75 years; baseline World Health Organization (WHO) performance status ≤3; life expectancy of at least 9 weeks; adequate bone marrow function (leukocytes >4000/mm^3, platelets >100000/mm^3); adequate renal and hepatic functions (serum creatinine <160 μmol/l, bilirubin <30 μmol/l and other liver function tests <2 times the normal upper range); no chemotherapy or extensive radiotherapy 4 weeks or less before FAA therapy (6 weeks for mitomycin C and nitrosoureas). Patients with unstable arterial hypertension or cardiovascular disease were also excluded. According to the normal procedure at our Institute, all patients were required to give written informed consent.

Pretreatment evaluation included a complete medical history and physical examination, chest X-ray, 12-lead electrocardiogram, complete blood cell counts, complete biochemical profile, prothrombin time, and urine analysis. Conventional radiology, ultrasound examination and CT scan were performed for tumor measurements, as indicated by clinical examination. Patients were treated as inpatients and were continuously monitored for blood pressure and pulse rate during FAA treatment and 6 h thereafter. Clinical, hematological and biochemical examinations were repeated before each FAA dose. When possible, tumor measurements were repeated every 6 weeks.

Evaluation of toxicity and efficacy

Toxic effects were assessed according to the National Cancer Institute criteria. Special attention was paid to the grading of arterial hypotension, which was as follows: grade 0, none or no change; grade 1, changes not requiring therapy, including transient orthostatic hypotension; grade 2, fluid replacement or other therapy required but no hospitalization; grade 3, therapy and hospitalization required, and toxicity resolved within 48 h after stopping the agent; grade 4, therapy and hospitalization required for more than 48 h after stopping the agent. Tumor response assessment was performed according to the WHO criteria.

Drug administration

FAA was provided by the Lyonnaise Industrielle Pharmaceutique (LIPHA, Lyon, France), as a freeze-dried powder in sterile vials (1 g/vial). The drug was reconstitued in 10 ml of sterile water and further diluted in 0.5 l of 0.9% saline. FAA was administered i.v. at a constant rate, over 6 h, without hyperhydration or urine alkalinization. During the first stage of this study, FAA administration was administered twice a week (every 72 h) for 6 consecutive weeks (this was termed "one course"), and thereafter according to the same schedule without discontinuation in the absence of severe toxicity and/or tumor progression. Cohorts of three patients were required at each dose level. The starting dose was 2.5 g/m^2. Dose escalation was guided by a nonlinear mathematical model [16]. Based on this model, the predicted maximum tolerated dose (MTD) was about 11 g/m^2. Five dose increments were planned, as follows: 2.5, 3.6, 5.4, 8.1 and 10.8 g/m^2. No intrapatient dose escalation was allowed until 2 newly included patients had been assessed at the highest dose level. During the last phase of this study, it was decided to optimize the treatment schedule by reducing the time interval between FAA dosages from 72 to 48 h in preference to increasing the FAA dose further.

Pharmacokinetics

Plasma and urine collection for pharmacokinetics

Heparinized blood samples (2 ml) were collected immediately pre-dose (time 0), and at 2, 4, and 6 h during drug infusion. After the end of infusion, samples were taken at 0.25, 0.5, 0.75, 1, 2, 4, 6, 12, and 24 h. Blood was immediately centrifuged at 2000 x g for 15 min, and the plasma was stored at −20° C until analysis. Urine was collected every 6 h. The volume was measured, and an aliquot of 10 ml was stored at −20° C until analysis.

FAA HPLC assay in plasma and urine

FAA concentrations were determined by HPLC. Briefly, 100 μl of HCl (1 *N*) and 50 μl of the internal standard (LM-2320, 0.5 mg/ml in methanol; LIPHA) were added to 1 ml of the biological sample. After mixing, the biological fluid was extracted with 5 ml of ethyl acetate. The organic phase was separated by centrifugation (2000 *g*, 10 min), and evaporated under nitrogen. The dry residue was reconstituted with 200 μl of the mobile phase, and 25 μl was injected onto a HPLC system composed of an octadecylsilane column (Nucleosil, 300 × 3.9 mm, 10 μm; SFCC, Neuilly-Plaisance, France) protected by a precolumn, with UV detection set at 300 nm. The mobile phase was composed of a 10 m*M* sodium acetate buffer (pH 4) and methanol (40:60, v/v) at a flow rate of 1.3 ml/min. In these conditions, the retention times of FAA and internal standard were 4.7 and 6.3 min, respectively.

Pharmacokinetic parameters determination

FAA plasma concentrations were analyzed using both model-independent and model-dependent procedures. Model-independent parameters included the following: the actual concentration at the end of i.v. infusion (C_{max}); the total area under the plasma concentration-versus-time curve (AUC) determined by the trapezoidal method to infinity; the mean residence time (MRT), which corresponds to the time for 63% of the drug to be eliminated from the plasma; the volume of distribution at steady state (V_{dss}) calculated according to the statistical moment theory; and the total body clearance, calculated as dose/AUC. For model-dependent analysis, FAA plasma concentrations were fitted to a two-compartment model with constant i.v. infusion, using a nonlinear regression program (PCNONLIN, Statistical Consultants, Lexington, Ky., USA). Results are expressed as mean ± SEM.

Results

Patient characteristics

Sixteen patients were entered on this phase I study, and a total of 130 doses of FAA were administered. Patient characteristics are presented in Table 1. Fourteen patients were evaluable for toxicity and efficacy. One patient refused further treatment after the second FAA dose, because of severe toxicity (arterial hypotension and somnolence at 8.1 g/m^2 dose level).

Table 1 Patient characteristics

Median (range) age (years)	51 (35–66)
Sex M:F	9:7
Median performance status (WHO)	1
Tumor type	
Head and neck	4
Gynecologic	3
Melanoma	2
Gastrointestinal	2
Other	5
Prior therapy	
Chemotherapy	16
Radiotherapy	11

Dose escalation and toxicity

Overall toxicity per dose level is summarized in Table 2. Since no significant toxicity was observed at 2.5 g/m^2 and 3.6 g/m^2 (6-h i.v. infusion), the FAA doses were subsequently escalated to 6.4 and 8.1 g/m^2, based on clinical tolerance and preliminary pharmacokinetic results confirming the good predictive value of our mathematical model in predicting for the maximum concentrations achieved (see Table 3 below) [16].

Since the first 4 patients did not experience any significant toxicity, it was decided to optimize the FAA schedule by reducing the interval between two doses to 48 h. Two patients safely received this modified protocol at 6.4 g/m^2 with neither severe toxicity nor evidence of drug accumulation. Four new patients were subsequently treated according to a three-times-a-week FAA schedule at 8.1 g/m^2 (i.e., every 48 h). Overall, 8 patients were treated at 8.1 g/m^2 and received a total of 71 doses, with a median of 7 doses per patient.

As detailed in Table 2, arterial hypotension, somnolence, and gastrointestinal side effects (diarrhea and vomiting) were the predominant toxicities. All clinical manifestations developed concomitantly with drug administration and usually resolved once the drug was discontinued. These symptoms appeared to be attenuated by lengthening the duration of the FAA infusion from 6 h to 7 h in 3 patients. Two patients exhibited severe hypotension requiring prolonged duration of drug infusion and also the administration of a macromolecule (Plasmion, Bellon Laboratory, Neuilly Sur Seine, France). One patient experienced severe but reversible lethargy during the fifth drug infusion at a dose of 8.1 g/m^2. Patient 15 experienced a severe toxicity characterized by somnolence 1 h after the initiation of the first FAA infusion, and arterial hypotension 3 h later, which did not improve despite a reduction in the FAA infusion rate. Hypotension was associated with oliguria, cardiovascular overload, and renal insufficiency (grade 2), which required macromolecule administration and vigorous diuretic and vasopressive treatments. The patient recovered his baseline neurocortical, renal and hemodynamic status 24 h later.

Table 2 Toxicity of flavone acetic acid (NCI criteria)

	FAA dose level (g/m^2)/interval of drug administration (h)				
	2.5/72 h	3.6/72 h	6.4/48 h	8.1/72 h	8.1/48 h
No. of patients/no. FAA doses	3/18	3/18	2/23	4/50	4/21
NCI grade					
Somnolence					
1	–	–	1	1	1
2	–	–	–	2	1
3	–	–	–	1	–
Hypotension					
1	–	–	1	2	1
2	–	–	–	1	–
3	–	–	–	–	1
Diarrhea					
1	–	–	–	1	1
2	–	–	–	2	1
3	–	–	–	–	–
Vomiting					
1	–	–	–	–	–
2	–	–	–	2	1
3	–	–	–	–	3
Myalgia					
1	–	–	–	1	1
2	–	–	–	1	1
3	–	–	–	–	–
Anemia					
1	–	–	–	–	–
2	–	–	–	2	–
3	–	–	–	–	–
Leukopenia					
1	–	–	–	2	1
2	–	–	–	–	–
3	–	–	–	–	–

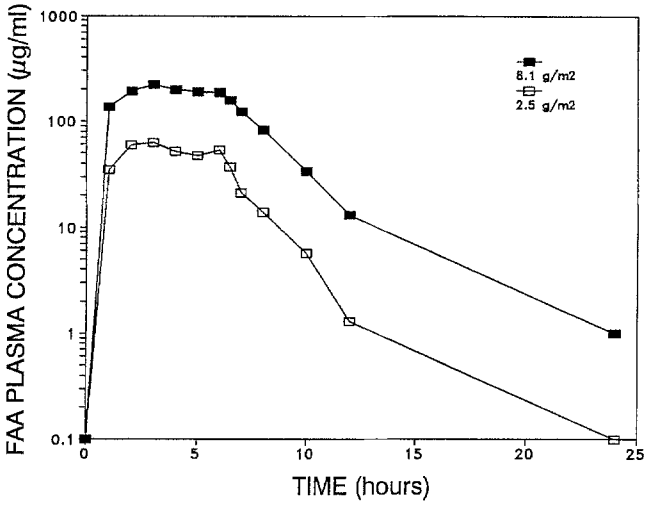

Fig. 1 Representative flavone-8-acetic (FAA) plasma concentrations versus time profiles at 2.5 g/m^2 (*open squares*) and 8.1 g/m^2 (*solid squares*) during and after a 6-h i.v. infusion

After this severe episode of acute toxicity, FAA phase I was definitively discontinued.

As expected from previous clinical studies [12–14], hematotoxicity was mild and infrequent. Most of the patients experienced asthenia after the third FAA infusion, and their general status did not improve during the FAA therapy, which suggests that fatigue might be a cumulative side effect. Myalgia, hot flushes, diffuse abdominal pain and blurred vision were common, although not severe, side effects.

Our experience indicates that the optimal schedule for FAA treatment might be infusion of 8.1 g/m^2 three times a week.

Pharmacokinetics

Complete pharmacokinetic data were obtained for the first course in 16 patients at FAA doses ranging from 2.5 to 8.1 g/m^2. Partial pharmacokinetic data, i.e., FAA concentration before and after the 6-h i.v. infusion were also obtained during 106 courses (Table 3). Representative FAA plasma concentration versus time profiles are presented in Fig. 1 at the starting dose (2.5 g/m^2) and at the highest dose reached in this phase I study (8.1 g/m^2).

Pharmacokinetic data are summarized in Table 3. The mean terminal half-life was 3.1 h, and the mean residence time (MRT) was 6.2 h. The total body clearance was 5.0 l h^{-1} m^2 , and the volume of distribution at steady state (V_{dss}) was 38 l/m^2. Peak plasma levels ranged from 39 to 449 and increased in proportion to the dose (r = 0.59, P <0.001, n = 106). The maximum concentrations predicted from a previous mathematical model [16] were in good agreement with the FAA concentrations measured (Table 3). Plasma area under the plasma versus time curves (AUC) increased linearly with dose levels administered (Fig. 2).

Whether the drug was administered every 3 days or every 2 days, no accumulation was noted in any patient, even at the highest dose administered (8.1 g/m^2). Depicted in Fig. 3 are the FAA plasma concentrations at the end of seven consecutive administrations in a representative patient who received 8.1 g/m^2 every 2 days, which show that there is no accumulation with this schedule.

The mean 24-h urinary excretion of unchanged drug was 11.2% of the dose administered. In one patient, pleural fluid obtained 3 days after the administration of FAA (8.1 g/m^2) contained a high drug concentration (170 µg/ml), while a simultaneous plasma sample did not show any detectable FAA.

Table 3 Flavone-8-acetic pharmacokinetic parameters

Patient no.	Dose (g/m^2)	Q Days	No. i.v.	Total dose (g/m^2)	Predicted C_{max}[a] (µg/ml)	FAA Conc. (µg/ml) First	Last	AUCo-oo (µg.h/ml)	MRT i.v. (h)	Total clearance l/h/m^2	Volume Vdss (l/m^2)	Terminal half-life (h)
1	2.5	3	5	12.5	98	52	97	371	1.7	6.7	32	0.7
2	2.5	3	6	15.0	98	39	30	368	7.2	6.7	69	
3	2.5	3	6	15.0	98	132	157	1247	7.2	2.0	21	
4	3.6	3	6	21.6	153	58	61	130	1.6	27.6	130	0.3
5	3.6	3	6	21.6	153	145	126	1199	5.4	3.0	25	4.0
6	8.1	3	18	145.8	408	152	222	1509	3.3	5.3	34	2.7
7	8.1	3	6	48.6	408	303	205	2862	7.2	2.8	29	
8	8.1	3	12	97.2	408	449	468	4241	7.2	1.9	20	
9	8.1	3	11	89.1	408	201	165	1899	7.2	4.2	44	
10	6.4	2	10	64.0	307	260	88	2456	7.2	2.6	27	
11	6.4	2	12	76.8	307	376	345	4510	10.8	1.4	20	7.0
12	8.1	2	7	56.7	408	352	135	3470	5.3	2.3	20	4.2
13	8.1	2	2	16.2	408	185	103	1747	7.2	4.6	47	
14	8.1	2	6	48.6	408	378	296	3570	7.2	2.2	23	
15	8.1	2	4	32.4	408	305	242	2344	5.7	3.4	30	2.2
16	8.1	2	4	32.4	408	242	305	2122	8.3	3.8	43	4.0
							Mean		6.2	5.0	38	3.1
							SEM		0.6	1.5	7	0.7

[a] Maximum concentration based on a mathematical model [16]

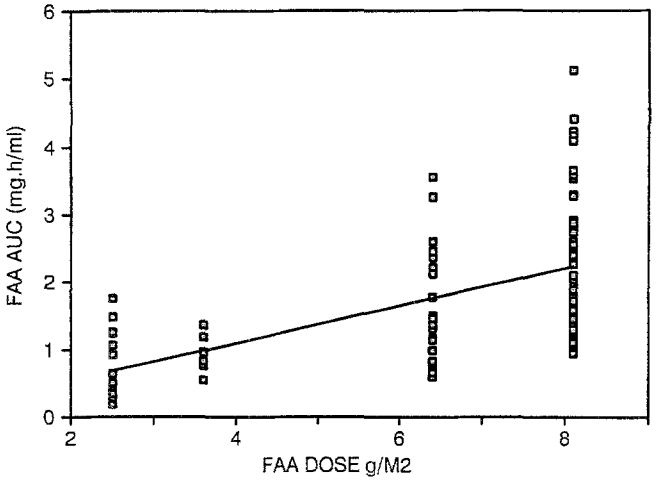

Fig. 2 Area under the plasma versus concentration curves (AUC) for FAA as a function of FAA dose (g/m^2) (y = 0.2754X, r = 0.59, P <0.001, n = 106)

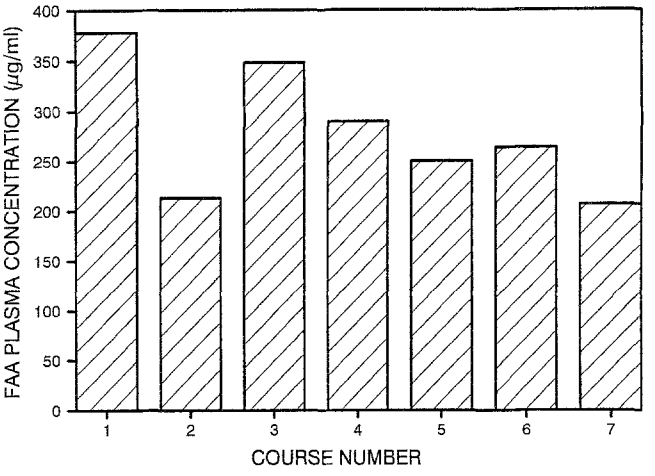

Fig. 3 Plasma concentrations at the end of the 6-h i.v. infusion in a representative patient receiving 8.1 g/m^2 of FAA every 2 days

Antitumor efficacy

With a median of seven FAA administrations per patient, no objective response was observed. All patients exhibited progressive disease during therapy.

Discussion

FAA is a synthetic compound with a unique pattern of activity in a broad spectrum of murine transplantable solid tumors but poorly active in rapidly growing hematological tumor models [1–4]. The mechanism of action of FAA is complex, multifactorial, and probably dependent on the tumor model under scrutiny. This compound is thought to act as an immune modulator or as an antivascular agent that induces a transient reduction in tumor blood flow (reviewed in [4]).

Up to now, FAA has been used in clinical phase I studies on the basis of preclinical pharmacokinetic data that indicated that high-dose concentrations and prolonged exposure were critical factors in determining the activity and toxicity of the drug. Zaharko et al. [11] defined a therapeutic window between 100 and 600 µg/ml. Previous phase I studies explored weekly schedules using different drug infusion durations: 1 h or 3 h in the study by Weiss et al. [13], and 1 h, 3 h or 6 h in the studies by Kerr et al. [12] and Halvin et al. [14]. These investigators used urine alkalinization by sodium bicarbonate as a means of preventing FAA crystallization in renal tubules. However, the process of alkalinization could have affected FAA activity, since Futami et al. [17] showed that the immunomodulatory properties of FAA in mice were inhibited by the alkalinization procedure via pharmacokinetic interactions. With these data in mind and on the basis of the nonlinear mathematical model proposed by Gouyette et al. [16], we decided to optimize FAA drug administration using a multiple weekly schedule without alkalinization.

Sixteen patients were entered in this phase I study, in which a total of 130 doses were administered. The median number of doses per patient was 6 (range 2–8). Ten patients were given FAA twice a week at doses ranging from 2.5 to 8.1 g/m^2. During the second phase of the study, 6 additional patients received FAA according to a schedule prescribing three infusions weekly at doses ranging from 6.5 to 8.1 g/m^2. The pattern of toxicity observed in this study closely resembled that described in previously published phase I studies using administration by slow infusion according to a weekly schedule [12–14]. Diarrhea, acute hypotension, sedation and asthenia were frequent, dose-related, and, in some patients, dose-limiting toxicities. In the study by Weiss et al. [13] the MTD was reached at 6.4 g/m^2 given as a 3-h infusion, with hypotension and asthenia being the dose-limiting toxicities. In the study by Kerr et al. [12] diarrhea and hypotension determined the MTD at a dose level of 10 g/m^2. In our experience, a schedule with 8.1 g/m^2 three times a week could be recommended as optimal treatment. Prolonging the drug infusion failed to prevent recurrence of drug-induced hypotension despite an attenuation of the drop in blood pressure. Asthenia was a cumulative toxicity in the study of Weiss et al. [13] and led to the discontinuation of treatment. Similar findings were observed in our study. No case of hepatotoxicity was recorded. The modification of the number of drug infusions in the schedule did not produce any changes in the pattern of toxicity. This is consistent with our pharmacokinetic data, which confirmed the absence of drug accumulation. Apparently, the absence of alkalinization cannot account for an increased risk of renal toxicity: the only case reported in our study was associated with dramatic hemodynamic failure and promptly resolved. Thus the hypothesis of FAA drug precipitation cannot be upheld. This lack of nephrotoxicity was also found in a recently published phase I study by Olver et al. [15] who gave a 12-h infusion every 3 weeks.

In accordance with the results recorded by other investigators [14, 15], FAA pharmacokinetics was shown to be linear between the 2.5 and 8.1 g/m^2 dose levels. Previous

studies have revealed nonlinear pharmacokinetics for this compound in rodents [18] and in humans [13]. This apparent discrepancy appears to be related to the fact that the clearance of the drug in humans is higher at lower FAA doses (<2 g/m^2) but appears to stabilize at higher doses [14]. As only relatively high doses were explored in this phase I trial, higher clearance values were therefore not observed.

FAA plasma concentrations achieved in this phase I trial are well within the values found for mice at efficacious doses [18]. Moreover, retention of high FAA concentrations in the pleural fluid appears to indicate that FAA does indeed reach the target tissue in sufficient concentrations. Although FAA reaches potentially antitumor concentrations in both plasma and target tumor tissues in humans, it failed to exhibit any antitumor efficacy both in this study and in other studies [19, 20]. These interspecies differences could be due to metabolism [7] or to the production of cytokines, which appears to be different in man and in the mouse [21]. This trial has also shown that it was feasible to use pharmacokinetic guidance to reach a predetermined target concentration, based on a mathematical model, during this phase I study [16].

In accordance with previous phase I and phase II studies [12, 13, 19, 20], FAA was also found to be inactive in the present study despite drug schedule optimization. Interestingly, one partial response was reported by Olver et al. [15] in a patient with renal cancer, which is a tumor type usually proposed for treatment with biological response modifiers. FAA is currently being investigated for a potential synergistic effect with interleukin 2 (IL2) [22]. Our study could help to define an optimal combination schedule of therapy with FAA and IL2 or other cytokines.

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